American Journal of Hematology 54:84–92 (1996)

LETTERS AND CORRESPONDENCE

Letters and correspondence submitted for possible publication must be identified as such. Text length must not exceed 500 words and five bibliographic references. A single concise figure or table may be included if it is essential to support the communication. Letters not typed double-spaced will not be considered for publication. Letters not meeting these specifications will not be returned to authors. Letters to the Editor *are utilized to communicate a single novel observation or finding.* Correspondence *is to be used to supplement or constructively comment on the contents of a publication in the journal and cannot exceed the restrictions for* Letters to the Editor*. The Editor reserves the right to shorten text, delete objectional comments, and make other changes to comply with the style of the journal. Permission for publication must be appended as a postscript. Submissions must be sent to Paul A. Chervenick, M.D., Associate Editor,* American Journal of Hematology*, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Suite 3157, Tampa, FL 33612-9497 to permit rapid consideration for publication.*

Case of Schwachman's Syndrome With Intermittent Neutropenia and Lymphocyte Subset Disturbances

To the Editor: Schwachman's syndrome, a familial disease transmitted as an autosomal-recessive trait, is characterized by moderate chronic neutropenia, marked marrow hypocellularity, occasional thrombocytopenia and anemia, metaphyseal dysostosis of tubular bones, pancreatic fatty infiltration, and accompanying pancreatic insufficiency with absence of pulmonary and sweat elecrolyte pathology. Steatorrhea and growth failure are prominent. Pancreatic enzyme replacement may compensate for pancreatic insufficiency, but no therapy has been fully effective on the hematologic abnormalities.

We report on a 6-year-and-9-month-old white male with Schwachman syndrome, admitted with complaints of stunted growth, distended abdomen, and fatty diarrhea. He was $<$3rd percentile with a McLaren scoring of 5. His liver extended 1.5 cm below the costal margin; his right iliac–malleol length was 2 cm shorter than the left. Roentgenograms revealed right femur neck shortness, acetabular hypoplasia, and infantile vertebrae.

Fat globules and fatty acids were positive in stool specimens and tripsin activity, and *Giardia* trophozoites were absent in repeated duodenal juice and stool examinations. Repeated sweat test chemistry was found normal (median Na, 30 mEq/l; Cl, 10 mEq/l). History, and physical and radiologic examinations, revealed that the child was generally free of pulmonary disease. Following informed parental consent, endoscopic examination of the small intestine disclosed only mucosal edema. An abdominal CT scan [2] showed fatty infiltration of the pancreas (Fig. 1).

During hospitalization, he presented with intermittent neutropenia (median, 1.1×10^9/l) in cycles of 3 weeks, instead of the moderate chronic neutropenia characteristic of Schwachman syndrome, and with moderate marrow cellularity during neutropenic periods, with normal maturity and ratio attained before the advent of each neutropenic cycle. However, there was no intense myelopoiesis beginning with the advent of neutropenia, and the typically elevated monocytes at the nadir of the neutrophil count were

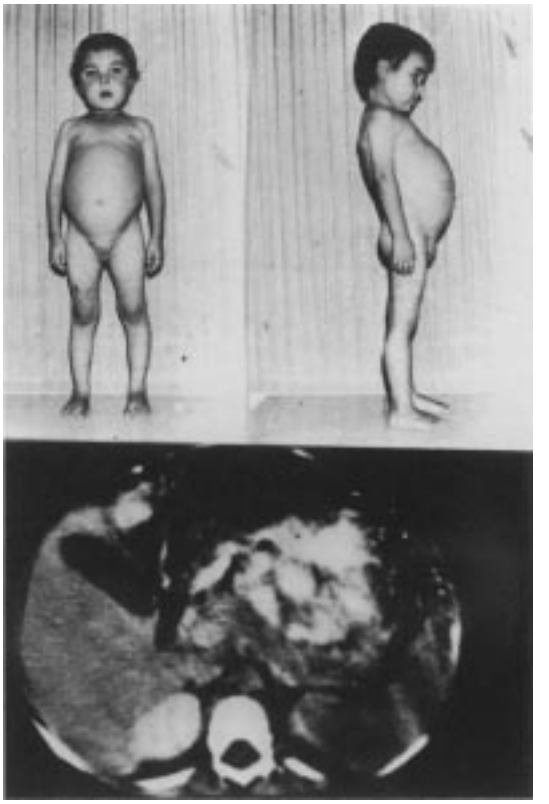

Fig. 1. The case and the fatty infiltration of the pancreas.

encountered in the present case, as seen in the ill-defined disease of cyclic neutropenia which is characterized with fever and oral ulcers in older children [1]. In addition, an immune-deficient state was also disclosed, with a median T4/T8 ratio of 0.40: 12% (low) T-helper and 30% T-suppressor cell counts. There was normal B-lymphocyte count, but also hypoimmunoglobulinemia with median serum immunoglobulin values of IgA, 11 mg/dl; IgM, 17 mg/dl; IgG, 107 mg/dl; and normal IgE our laboratory normal ranges are close to Hong's International Reference Standard Values) [3].

The patient's glomerule filtration rate, acid-loading test, and thyroid functions were normal. Other systemic and routine hematologic and biochemical findings were remarkable. No medication was instituted during his stay in the hospital.

We did not come across such disturbances as were seen in the present case in other cases with Schwachman's syndrome reported formerly, except in the case of Brueton et al. [4], presenting with cyclic neutropenia and variability in immunoglobulins.

The patient returned for a single follow-up examination 3 months after discharge with pancreatic enzyme replacement. His findings suggested a

constitutional immunodeficiency state rather than a secondary phenomena to malnutrition.

Figen Oksel
Baha Taneli
Department of Pediatrics, Faculty of Medicine, Ege University, Izmir, Turkey

References

1. Corrigan JJ Jr: Disorders of the leukocytes. In Behrman RE, Kliegman RM, Nelson WE, Vaugmann RC III (eds): "Nelson Textbook of Pediatrics," Ed 14. Philadelphia: W.B. Saunders Co.: 1992, p. 1266.
2. Robberecht E, Nachtegaele F, Rattinghe R, Afschrift M, Kunnen M, Verhaaren R: Pancreatic lipomatosis in the Schwachman-Diamond syndrome: Identification by sonography and CT-scan. Pediatr Radiol 15:348, 1985.
3. Hong's International Reference Standard Values: Springfield, VA: NCI Immunoglobulin Reference Center.
4. Brueton MJ, Mauromichalis J, Goodchild MC, Anderson CM: Hepatic dysfunction in association with pancreatic insufficiency and cyclical neutropenia: Schwachman-Diamond syndrome. Arch Dis Child 52:76, 1977.

Prothrombin Deficiency and Hemorrhage Associated With a Lupus Anticoagulant

To the Editor: Lupus anticoagulant (LA) is a common clotting abnormality found in patients with systemic lupus erythematosus (SLE). Although LA is responsible for an "in vitro" hypocoagulability, it is not associated with an "in vivo" hemorrhagic tendency. In contrast, it is now well-established that LA is a risk factor for thrombosis [1]. We describe a patient with SLE and LA who developed hemorrhagic tendencies as a consequence of a clotting factor II (prothrombin) deficiency.

A 12-year-old girl was referred because of abnormal hemorrhage following cutaneous biopsy. She had had a 2-month history of localized erythematous skin lesions in the malar region and bridge of the nose, frequent epistaxis, and easy bruisability. She was not receiving any medications. There was no family history of abnormal bleeding. Laboratory examination showed a leukocyte count of 2,900/mm^3 with 1,000 lymphocytes/mm^3, hemoglobin 12.4 g/dl, and platelet count of 102,000/mm^3. Prothrombin time (PT) was 23 sec (normal values (NV), 12.5–13.5 sec), activated partial thromboplastin time was 47\sec (NV, 26–35 sec), thrombin time was 20 sec (NV, 18–22 sec), and factor II clotting activity was at 30% (NV, 60–140%). Clotting assay results for other coagulation factors were within normal ranges. Factor II inhibitor assay was negative. Diluted Russell's viper venom time (DVV test, American Diagnostica,) was 73 sec (NV, 28–48 sec), and platelet neutralization procedure (DVV Confirm, American Diagnostica) was positive. Anticardiolipin antibody test (ACA, Cheshire Diagnostic Ltd., UK) gave results of IgG 46.2 (NV, $<$15) and IgM 15.9 (NV, $<$13). Antinuclear antibodies (ANA) were positive (1:160 dilution), anti-native DNA antibodies were positive (1:80 dilution), C_3 was 0.35 g/l (NV, 0.5–1.2 g/l), and C_4 was 0.01 g/l (NV, 0.2–1.2 g/l).

Skin bleeding stopped using local measures, and blood derivatives transfusion was not required. She was started on deflazacort therapy (30 mg a day given in a single oral dose for 7 days, 22.5 mg a day for 7 days, and then maintenance treatment with 15 mg per day). One month later, physical examination revealed a marked improvement of the skin lesions. The patient was free of bleeding complications. Laboratory data revealed the following: platelet count of 103,000/mm^3, normal blood coagulation with factor II 80% and LA-negative, anticardiolipin antibodies-negative, ANA-positive (dilution 1:80), and anti-native DNA antibody-positive (dilution 1:40). Five months after diagnosis, corticoid doses were increased because SLE showed clinical evidence of activity (oral ulcers, diffuse hair loss, and arthritis). However, blood coagulation test results remained within normal ranges.

Most patients with LA do not bleed abnormally. When this happens, an abnormality other than LA must be suspected. Anticoagulants directed against von Willebrand factor, factor VIII, factor IX, factor XI, and fibrin polymerization have been described in patients with SLE [2]. Another associated condition which may predispose to hemorrhage is a specific factor II deficiency [2,3]. Although minimal to moderate prolongation of PT can be accounted for by LA, the finding of a substantially prolonged PT represents presumptive evidence of an associated factor II deficiency. The interrelationship between LA and factor II deficiency is not clearly understood. There is evidence that several LA IgG preparations can bind directly to prothrombin without neutralizing its coagulant activity. It is also recognized that hypoprothrombinemia is associated with a concordant depletion of plasma prothrombin antigen. The deficiency is presumed to be secondary to a rapid clearing of prothrombin/antiprothrombin complexes in the liver [4]. Finally, most cases respond to corticosteroid therapy with or without the administration of fresh-frozen plasma [5].

We have described a patient with SLE who developed hemorrhagic tendencies as a consequence of a factor II deficiency. The presence of LA and hypoprothrombinemia was confirmed by several commonly-used tests. In addition, a circulating neutralizing antibody to factor II was not detected. Our patient improved promptly after initiation of corticoid therapy. Reevaluation 1 month later showed that all "in vitro" coagulation test results had returned to normal. After a follow-up of 5 months, SLE showed activity, but blood coagulation test results remained normal. Thus, LA-associated hypoprothrombinemia seems to have a high sensitivity to corticoid therapy and a weak correlation with the clinical evolution of SLE.

Our case indicates that this unusual complication of LA should be considered in the differential diagnosis of patients who have abnormal bleeding. We suspect that this complication may be more common than is suggested by the existing literature.

Enric Grau
Esperanza Real
Emilio Pastor
Jose Ivorra
Esther Quecedo
Departments of Hematology, Rheumatology, and Dermatology, Hospital Luis Alcanyis, Xativa, Spain

References

1. Hughes GRV: The antiphospholipid syndrome: Ten years on. Lancet 342:341–344, 1993.
2. Feinstein DI, Francis RB: The lupus anticoagulant and anticardiolipin antibodies. In Wallace DJ, Hahn BH (eds): "Dubois' Lupus Erythematosus." Wallace DJ, Hahn BH, eds. Philadelphia: Lea & Febiger, 1993, pp 246–253.
3. Eberhard A, Sparling C, Sudbury S, Ford P, Laxer R, Siverman E: Hypoprothrombinemia in childhood systemic lupus erythematosus. Semin Arthritis Rheum 24:12–18, 1994.
4. Permpikul P, Mohan Rao LV, Rapaport SI: Functional and binding studies of the roles of prothrombin and B_2-glycoprotein I in the expression of lupus anticoagulant activity. Blood 83:2878–2892, 1994.
5. Bernini JC, Buchanan GR, Ashcraft J: Hypoprothrombinemia and severe hemorrhage associated with a lupus anticoagulant. J Pediatr 123:937–939, 1993.

Tumor Lysis Syndrome in a Case of Chronic Lymphocytic Leukemia Induced by High-Dose Corticosteroids

To the Editor: Tumor lysis syndrome (TLS) results from massive tumor-cell destruction that usually occurs hours or days after the beginning of

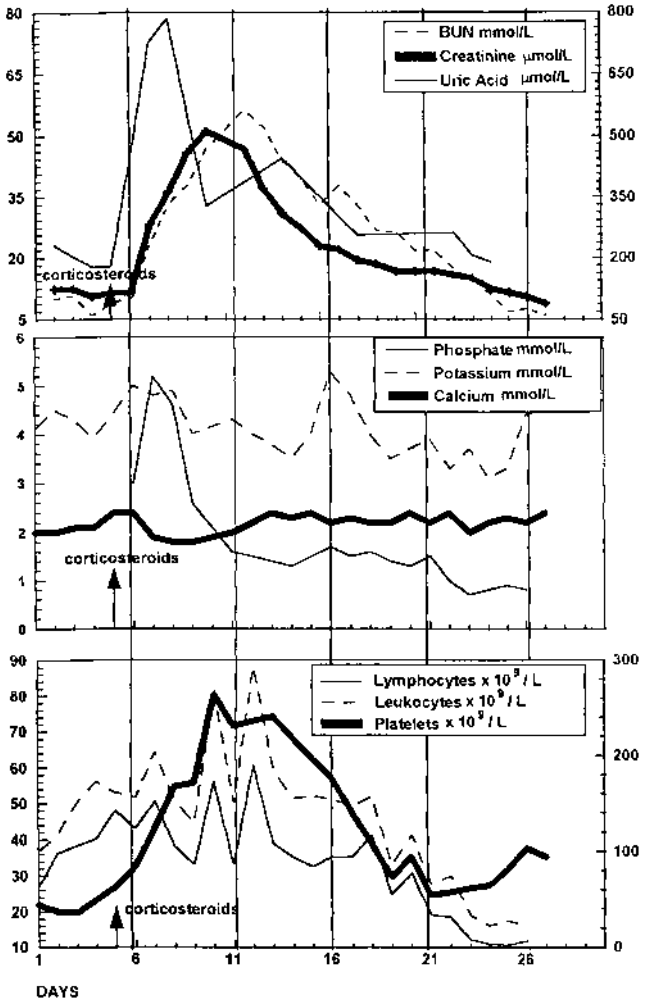

Fig. 1. Biochemical and hematological parameters of the patient described before and after administration of high-dose corticosteroids.

cytotoxic-specific therapy [1]. As a result of this major tumor cytorreduction, severe hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia may occur [1]. This syndrome usually occurs in patients with tumors highly sensitive to the cytotoxic chemotherapeutic agents employed, such as high-grade lymphomas and acute leukemias. Although TLS was reported in high-grade lymphoproliferative disorders after the use of corticosteroids [2], so far we have found no reports in the literature of TLS induced by corticosteroids used as a single agent in chronic lymphocytic leukemia (CLL).

A 44-year-old male had a diagnosis of CD5-positive B CLL made in 1993. The patient refused treatment and was lost to follow-up. In May 1995 he was diagnosed with legionella pneumonia, as confirmed by lung biopsy and serology. At the time of this admission he had cervical and axillary bilateral lymphadenopathy and splenomegaly. Laboratory studies showed WBC of 36.8×10^9/l, with 27.2×10^9/l lymphocytes and 45×10^9/l platelets. His creatinine consisted of 83 mmol/l, potassium 4.1 mmol/l, magnesium 0.8 mmol/l, calcium 2.0 mmol/l, glucose 6.2 mmol/l, and LDH 3.6 μkat/l. Creatinine clearance was 74.7 ml/min. In an attempt to avoid endotracheal entubation the patient received two doses of 2 g of methylprednisolone endovenously for 2 consecutive days. Forty-eight hr after corticotherapy, he developed TLS with a creatinine of 283 micromol/l, BUN of 23.4 mmol/l, uric acid of 726 micromol/l, potassium of 5.0 mmol/l, magnesium of 1.3 mmol/l, calcium of 2.4 mmol/l, and phosphate of 3.0 mmol/l (Fig. 1).

Abdominal ultrasound showed only ascites and splenomegaly at that time. He was then treated for legionella pneumonia with normalization of his renal function and metabolic abnormalities. His lymphadenopathies and splenomegaly disappeared, and his lymphocyte counts decreased significantly after the pulses of methylprednisolone.

The occurrence of TLS in patients with CLL was previously described with purine analogs such as fludarabine [3] and 2-chlorodeoxyadenosine [4], as well as with aggressive combination chemotherapy regimens [5].

This case illustrates, therefore, that high doses of corticosteroids can also produce TLS in CLL patients. Thus, before the administration of high-dose corticosteroid regimens to patients with CLL, one may consider instituting the usual precautions for patients at risk for TLS, such as hydration, urine alkalinization, and allopurinol administration.

Anelisa K. Coutinho

Grupo de Estudos en Medicina, Bahia, Brazil

Marcelo de O. Santos
Helio Pinczowski
Olavo Feher

Grupo de Altas Doses de Quimioterapia do Hospital, Samaritano-Sao Paulo, Sao Paulo, Brazil

Auro del Giglio

Department of Hematology, ABC Foundation School of Medicine, Sao Paulo, Brazil

References

1. Chasty RC, Liu-Yin JA: Acute Tumor lysis syndrome. Br J Hosp Med 49:488–492, 1993.
2. Loosveld OJL, Schouten HC, Gaillard CA, Blijham GH: Acute tumor lysis syndrome in a patient with acute lymphoblastic leukaemia after a single dose of prednisone. Br J Haematol 77:122–123, 1991.
3. Frame JN, Dahut WL, Crowley S: Fludarabine and acute tumor lysis in chronic lymphocytic leukemia. N Engl J Med 327:1396–1397, 1992.
4. Dann EJ, Gillis S, Polliak A, Rund D, Rachmilewitz E: Brief report: Tumor lysis syndrome following treatment with 2-chlorodeoxyadenosine for refractory chronic lymphocytic leukemia. N Engl J Med 329:1547–1548, 1993.
5. McCroskey RD, Mosher DF, Spencer CD, Prendergast E, Longo WL: Acute tumor lysis syndrome and treatment response in patients treated for refractory chronic lymphocytic leukemia with short-course, high-dose cytosine arabinoside, cisplatin, and etoposide. Cancer 66:246–250, 1990.

Detection of HTLV-I Proviral DNA by Fluorescence In Situ Hybridization

To the Editor: Human T-cell lymphotropic virus type I (HTLV-I) is the causative agent of adult T-cell leukemia (ATL) and of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The HTLV-I genome can be detected by several methods, including Southern blot hybridization [1], polymerase chain reaction (PCR) [2], in situ hybridization (ISH) [3], and PCR-ISH [4]. In this study, attempts were made to apply the fluorescence in situ hybridization (FISH) technique for the detection of integrated HTLV-I proviral DNA.

Peripheral blood mononuclear cells (PBMC) from 3 patients with ATL and 3 asymptomatic HTLV-I carriers, and four HTLV-I-infected cell lines (MT-I, MT-2, Ra-1, and ATL-1K), were examined. PBMC from 3 seronegative healthy persons and one HTLV-I uninfected cell line (TALL-1) were used as negative controls. A full-length HTLV-I probe pMT-2 (kindly provided by Dr. G. Franchini, Bethesda, MD) was used after biotin-labeling.

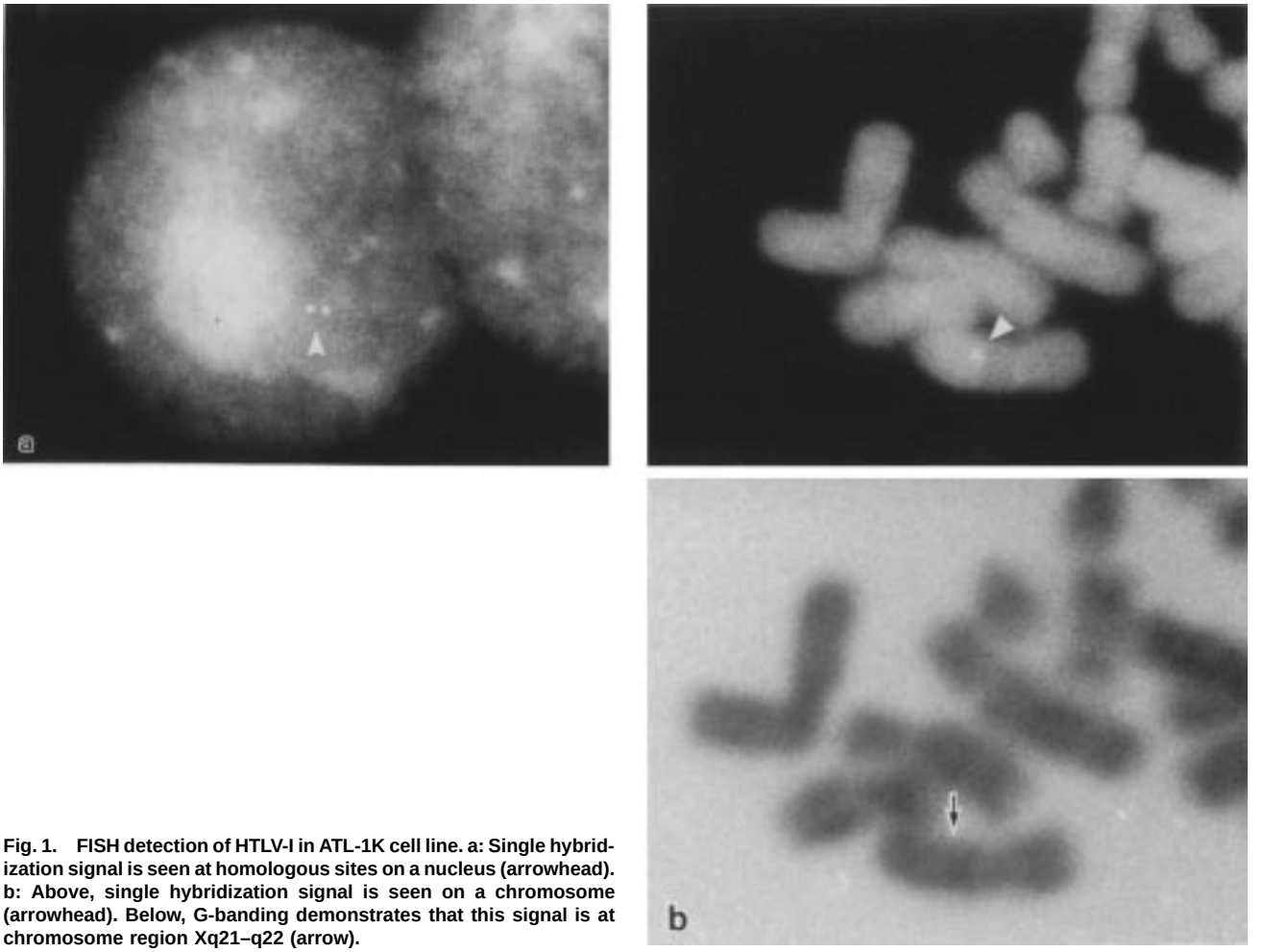

Fig. 1. FISH detection of HTLV-I in ATL-1K cell line. a: Single hybridization signal is seen at homologous sites on a nucleus (arrowhead). b: Above, single hybridization signal is seen on a chromosome (arrowhead). Below, G-banding demonstrates that this signal is at chromosome region Xq21–q22 (arrow).

Hybridization signals for the probe were cytochemically detected with fluorescein isothioctanate-avidin. One thousand nuclei without overlapping truncation were evaluated per sample. FISH signals were counted and photographed with an Olympus BH-2 microscope. The percentage of positive cells, which ranged from 57.5–95.5% in PBMC from ATL patients and virus-infected cell lines, was $<3.9\%$ in PBMC from HTLV-I carriers. The fresh samples from ATL patients and virus-infected cell lines showed multiple signals per cell, except for ATL-1K, which contained one signal per cell in most cells (Fig. 1a). In addition, we detected one hybridization signal of ATL-1K at chromosome region Xq21–q22 by FISH combined with G-banding (Fig. 1b). Although similar signals were seen in $<1\%$ of cells from seronegative control persons, they were interpreted as false-positive due to the background effect. The presence of multiple signals in these HTLV-I-infected cell lines was consistent with Southern blot analysis that showed multiple bands after *Eco*RI digestion (data not shown).

Yoshida et al. [5] demonstrated a monoclonal integration of the HTLV-I provirus in primary tumor cells of 88 ATL patients, and showed that integration of single intact HTLV-I provirus was typical. The sense riboprobe, complementary to viral DNA, can theoretically hybridize to one copy, but the conventional ISH technique is not sensitive enough to detect low copy numbers. In order to increase the sensitivity of ISH, PCR-ISH has recently been developed, and this technique demonstrated HTLV-I *tax* DNA in 1 of 5,000–10,000 PBMC from patients with HAM/TSP [4]. Detection of positive signals would be more difficult in HTLV-I carriers than in HAM/TSP patients, because the number of infected cells is small. Despite this, FISH allowed us to visualize one signal per nucleus in 2.1–3.9% of PBMC from virus carriers. Therefore, FISH appears to be highly sensitive for the detection of low HTLV-I proviral load, and may be useful for the identification of cellular localization of HTLV-I in HTLV-I-associated diseases such as uveitis, polymyositis, and arthropathy, as well as ATL and HAM/TSP. In addition, mapping of HTLV-I integration sites may provide clues to the interaction between cellular and viral sequences leading to these HTLV-I-associated diseases.

Yoshiki Uemura
Tetsuya Kubota
Tatsushi Miyagi
Jun Imamura
Ichiro Kubonishi
Hirokuni Taguchi
Isao Miyoshi
Third Department of Internal Medicine, Kochi Medical School, Kochi, Japan

Kiichi Shimizu
Shionogi Biomedical Laboratories, Osaka, Japan

References

1. Yoshida M, Miyoshi I, Hinuma Y: Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci USA 79:2031, 1982.
2. Kwok S, Ehrlich G, Poiesz B, Kalish R, Sninsky JJ: Enzymatic amplification of

HTLV-I viral sequences from peripheral blood mononuclear cells and infected tissues. Blood 72:1117, 1988.
3. Greaves MF, Verbi W, Tilley R, Lister TA, Habeshaw J, Guo HG, Trainor CD, Robert-Guroff M, Blattner W, Reitz M, Gallo RC: Human T-cell leukemia virus (HTLV) in the United Kingdom. Int J Cancer 33:795, 1984.
4. Levin MC, Fox FJ, Lehky T, Walter M, Fox CH, Flerlage N, Bamford R, Jacobson S: PCR-in situ hybridization detection of human T-cell lymphotropic virus type I (HTLV-I) *tax* proviral DNA in peripheral blood lymphocytes of patients with HTLV-I-associated neurologic disease. J Virol 70:924, 1996.
5. Yoshida M, Seiki M, Yamaguchi K, Takatuki K: Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia virus in the disease. Proc Natl Acad Sci USA 81:2534, 1984.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia After Therapy for Langerhans Cell Histiocytosis

To the Editor: Langerhans cell histiocytosis (LCH) is a group of poorly understood disorders characterized by infiltration of involved tissues by Langerhans cells. LCH may present with a solitary bone lesion or a multisystem, life-threatening disorder. Most patients with systemic disease usually receive chemotherapy. Recently, the association of LCH with a second neoplasm has been reported. We report a case of acute lymphoblastic leukemia (ALL) with the Philadelphia (Ph) chromosome which developed after radiotherapy and chemotherapy for LCH.

A 9-year-old boy had a right cervical mass partially resected in April, 1986 [1]. The diagnosis of LCH was made by standard histiopathology and immunochemistry. Three months later, the remaining mass enlarged, and subtotal resection was performed. He then developed a presternal soft-tissue mass and was treated with radiotherapy (29.62 Gy), followed by chemotherapy consisting of vinblastine (VLB; 0.1–0.3 mg/kg, weekly for five doses), 6-mercaptopurine (6-MP; 2 mg/kg, daily for 6 months), and prednisolone (PSL; 1 mg/kg, daily for 6 months, then tapered). A complete remission was maintained for 7 years. He was readmitted in June, 1993 because of fever, epistaxis, pallor, and purpura on his legs. Laboratory findings were as follows: Hb 8.8 g/dl, platelets 26×10^9/l, and WBC 340×10^9/l with 96% blasts. Bone marrow showed hypercellularity with 97.4% blasts with FAB-L1 morphology. Serum of lactate dehydrogenase was 3,404 IU/l. Blasts were negative for peroxidase; surface marker analysis revealed positivity for CD10, CD19, and CD34. Cytogenetic examination revealed all cells analyzed to be 46,XY,t(9;22)(q34;q11). A rearrangement of bcr-abl in the minor breakpoint region was shown by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. He was initially treated with the Japan Adult Leukemia Study Group (JALSG) ALL-90 protocol. No remission was obtained, and central nervous system (CNS) leukemia occurred in September, 1993. Despite whole-brain irradiation and high-dose chemotherapy, the patient died of multiple organ failure in February, 1994.

The association of LCH with a second neoplasm has been the subject of isolated case reports [2–4]. Egeler et al. [2] postulated that this association follows two distinct processes: reactive, and therapy-related. They reported that the simultaneous association of LCH with malignant lymphoma or lung carcinoma suggested a reactive process, while leukemias or other solid tumors developing after treatment of LCH were suggestive of a therapy-related process. Thus far, secondary acute myelogenous leukemia (AML) developing after treatment of LCH with VP16 [2–4] has been reported. However, VP16 was not used in our case.

On the other hand, secondary leukemias are rare in ALL [5]. In a Japanese survey for 301 cases of therapy-related leukemia/myelodysplastic syndrome, only 3 cases of Ph-positive ALL, including our case, were reported. A few cases of ALL have been reported in association with LCH [2,3], and this is the first case of ALL with the Ph chromosome after radiotherapy and chemotherapy for LCH. Our case is suggestive of a radiotherapy-associated leukemia. Cooperative studies of LCH patients may identify an association between LCH and acute leukemia, as well as any risk factors or predisposing agents.

Tetsuya Tatsumi
Chihiro Shimazaki
Shin-Ichi Araki
Yoshikazu Sudo
Noboru Yamagata
Eishi Ashihara
Hideo Goto
Tohru Inaba
Naohisa Fujita
Masao Nakagawa
Second Department of Medicine
Shin-Ichi Misawa
Third Department of Medicine
Shinsaku Imashuku
Division of Pediatrics, Children's Research Hospital, Kyoto Prefectural University of Medicine, Kyoto, Japan

References

1. Yoshihara T, Hibi S, Imashuku S, Sawada T: Primary eosinophilic granuloma of the cervical lymph nodes in a child: Report of a rare case with invasion into the soft tissue [in Japanese]. Jpn J Pediatr 91:3346, 1987.
2. Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME: Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer 71:865, 1993.
3. Arico M, Comelli A, Bossi G, Raiteri E, Piombo M, Egeler RM: Langerhans cell histiocytosis and acute leukemia: Unusual association in two cases. Med Pediatr Oncol 21:271, 1993.
4. Horibe K, Matsushita T, Numata S, Miyajima Y, Katayama I, Kitabayashi T, Yanai M, Sekiguchi N, Egi S: Acute promyelocytic leukemia with t(15;17) abnormality after chemotherapy containing etoposide for Langerhans cell histiocytosis. Cancer 72:3723, 1993.
5. Kapoor G, Bajpai S, Nair CN, Badrinath Y, Gladstone B, Advani SH: CALLA positive acute lymphoblastic leukemia after etoposide-based therapy for Ewing's sarcoma. Leuk Res 19:771, 1995.

Hemophagocytic Syndrome Responding to High-Dose Gammaglobulin as Presenting Feature of Sarcoidosis

To the Editor: The sporadic form of fulminant hemophagocytic syndrome (FHS) is an aggressive and often fatal disorder characterized by fever, jaundice, multiple organ failure, cytopenias, coagulopathy, and hypertriglyceridaemia [1]. The most striking histopathologic feature is the proliferation within lymph nodes and bone marrow of macrophages phagocytizing all sorts of blood cells. Sporadic FHS has been described in association with viral and bacterial infections, immunodeficiency, systemic lupus, Still's disease, and malignancies.

Treatment has been generally disappointing, although recently three reports described single patients responding to high-dose gammaglobulin therapy [2–4].

We recently observed a patient in whom FHS preceded a diagnosis of sarcoidosis, and i.v. gammaglobulin therapy was successful.

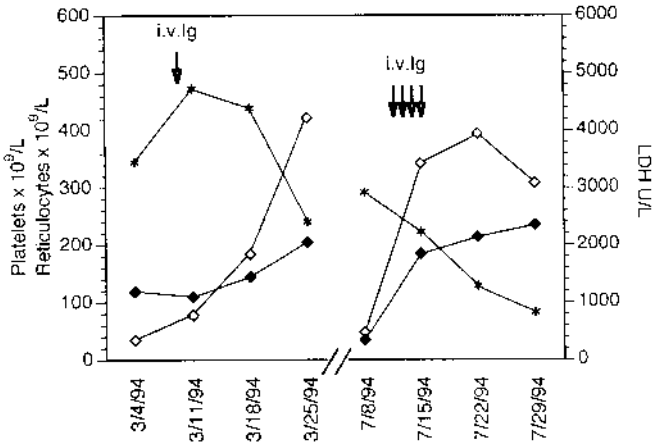

Fig. 1. Temporal changes in platelets (♦), reticulocytes (◇), and serum LDH intravenous i.v. Ig, high-dose i.v. gammaglobulin.

This patient, a 23-year-old female, was hospitalized at the beginning of March 1994 for an acute febrile illness. Investigation revealed anemia (Hb hemoglobin 6.3 g/dl), leukopenia (2.4×10^9 WBC/l with normal differential count), and mild thrombocytopenia (124×10^9 platelets/l). Based on elevated values of bilirubin (55.7 μM/l) and LDH (3,427 U/l) and low haptoglobin (<40 mg/dl), an acute hemolytic anemia was suspected. She received a single dose of i.v. gammaglobulin (10 g) and was started on prednisone therapy (100 mg/day). Three days later she was transferred to our institution. Physical examination revealed fever (39°C), splenomegaly (4 cm below the costal arch), and jaundice. Laboratory investigations (pancytopenia, clear signs of hemolysis, negative direct and indirect Coombs' test, and hypertriglyceridaemia) and bone-marrow aspirate (showing histiocytosis and haemophagocytosis of all types of marrow and blood cells) led to a diagnosis of FHS. The patient improved without further therapy, and all clinical and laboratory parameters normalized within 1 month (Fig. 1).

The subsequent clinical course was uneventful until July, when the patient was hospitalized again because the clinical and laboratory features of FHS recurred. Therapy with i.v. gammaglobulin (20 g × 4 days) was initiated, and 2 days later laboratory data began to improve, reaching normal values within 1 month. Meanwhile, chest X-ray revealed bilateral hilar adenopathy and a diffuse reticulonodular lung infiltrate suggesting a diagnosis of sarcoidosis. Lung function tests, gallium 67 chest scan, bronchoalveolar lavage, serum angiotensin-converting enzyme, and biopsy of scalene nodes were consistent with this diagnosis.

The patient undertook prednisone therapy that induced remission of sarcoidosis within 6 months. During this period she also received maintenance therapy with i.v. gammaglobulin (monthly injection of 20 g). After remission of sarcoidosis, no further gammaglobulin therapy was given, and FHS did not reappear.

Our observation adds further support to the hypothesis that i.v. gammaglobulin therapy may be truly effective in FHS, in that it induced remission in our patient both when associated with prednisone and when used as a single agent. The mechanisms of action of high-dose gammaglobulin are complex and include the blockade of histiocyte Fc receptors, reduction of activated T helpers, and increase of T-suppressor cell number. All these mechanisms of action are consistent with a possible effect of high-dose gammaglobulin in FHS, where hypercytokinemia and abnormal activation of histiocytes have a pathogenetic role.

Although it has never been reported previously, the association between FHS and sarcoidosis is not surprising, since both conditions seem to derive from an immune regulation defect characterized mainly by T-cell abnormalities and increased lymphokine production [5].

In conclusion, our observation confirms that i.v. gammaglobulin may be effective in FHS, and shows for the first time that this syndrome may be associated with sarcoidosis.

Carlo L. Balduini
Patrizia Noris
Institute of Internal Medicine and Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico San Matteo-University of Pavia, Pavia, Italy

Carlo Loni
Carlo Aiosa
Division of Medicine, Pietrasanta Hospital, Lucca, Italy

References

1. Cline MJ: Histiocytes and histiocytosis. Blood 84:2840, 1994.
2. Freeman B, Rathore MH, Salman E, Joyce MJ, Vitel P: Intravenously administered immune globulin for the treatment of infection-associated hemophogocytic syndrome. J Pediatr 123:479, 1993.
3. Fort DW, Buchanan GR: Treatment of infection-associated hemophagocytic syndrome with immune globulin. J Pediatr 124:332, 1994.
4. Gill DS, Spencer A, Cobcroft RG: High-dose gamma-globulin therapy in the reactive haemophagocytic syndrome. Br J Haematol 88:204, 1994.
5. Watson HG, Goulden NJ, Manson ML, McDermid G, Gray JA, Parker AC: Virus-associated haemophagocytic syndrome: Further evidence for a T-cell mediated disorder. Br J Haematol 86:213, 1994.

Sideroblastic Anemia Terminating in Chronic Myeloid Leukemia

To the Editor: Acquired refractory sideroblastic anemia (ARSA) frequently lasts for years without progression. However, over a 10–15-year period, about 10% of patients with ARSA develop acute myeloid leukemia. Also, a transformation of ARSA to acute lymphocytic leukemia has been described [1]. Evolution of ARSA into a chronic myeloproliferative disease is an exceptional finding. Only two cases of ARSA terminating in idiopathic myelofibrosis, and only one case of ARSA terminating in polycythemia vera, have been documented so far [2,3]. We describe the first case of typical ARSA terminating in Philadelphia (Ph) chromosome-negative and bcr-negative chronic myeloid leukemia (CML), with typical clinical and morphological features.

A 58-year-old man was admitted for evaluation of anemia on January 1991. Physical examination was unremarkable, with no hepatosplenomegaly. Laboratory examination at that time revealed: hemoglobin 5.7 g/dl, red blood cell count of 2.48×10^{12}/l, MCV 68.2 fl, reticulocytes 2%, platelets 335×10^9/l, and a leukocyte count of 6.4×10^9/l. Serum iron levels and saturation of transferrin were slightly increased. Serum ferritin concentration was 545 ng/ml (normal values, 27–300 ng/ml). Hemoglobin A1 concentration was normal, while hemoglobin A2 concentration was only slightly increased: 4.5% (normal values, 1.5–3.5%). The blood film showed a population of hypochromic red cells with anisocytosis and poikilocytosis, and hypogranular neutrophils with Pelger-Huet anomaly. A bone-marrow aspirate and biopsy showed increased cellularity as a result of erythroid hyperplasia. Prussian blue staining of the marrow showed pathologic ringed sideroblasts. Granulopoiesis was not altered and thrombopoiesis was normal, except for slight signs of dysmegakaryopoiesis (micromegakaryocytes). Marrow iron stores were increased, while significant fibrosis was absent. A diagnosis of ARSA was made, and

the patient received periodic transfusions of red cells, while the administration of folic acid and danazol gave only a transient benefit. Sixteen months after onset of the myelodysplastic syndrome (MDS), the patient presented marked splenomegaly. Laboratory examination revealed: hemoglobin 7.5 g/dl, platelets 200×10^9/l, and a leukocyte count of 26×10^9/l, with the following differential count: neutrophils, 70%; basophils, 2%; lymphocytes, 6%; promyelocytes, 3%; myelocytes, 10%; metamyelocytes, 6%; and blasts, 3%. A bone-marrow aspirate and biopsy showed a massive hyperplasia of granulocytes with normal maturation. Megakaryocytopoiesis appeared normal, while erythropoiesis was reduced, in the absence of significant fibrosis. The neutrophil alkaline phosphatase was markedly increased (score of 260). Cytogenetic analysis of the bone marrow revealed a normal karyotype. A detailed molecular study of the bcr gene, by Southern blot analysis of the patient's bone-marrow DNA, allowed us to exclude the presence of breakpoints in the M-bcr region [4]. Furthermore, the absence of the p190 as well as of the p210 chimeras was documented by reverse-transcriptase polymerase chain reaction assays performed on RNA extracted from the patient's bone marrow and peripheral leukocytes [4]. A diagnosis of Ph chromosome-negative and bcr-negative CML was made and the patient received hydroxyurea, which was effective in controlling the leukocyte count for about 1 year. In April 1993, the patient was referred to us for bone pain. Peripheral blood analysis revealed: hemoglobin 9.9 g/dl, platelets 68×10^9/l, and a sudden rise in the leukocyte count, to 125×10^9/l, with the following differential count: neutrophils, 41%; basophils, 4%; lymphocytes, 5%; monocytes, 2%; promyelocytes, 11%; myelocytes, 10%; metamyelocytes, 5%; and blasts, 22%. A bone-marrow aspirate revealed almost absent erythropoiesis and megakaryopoiesis, with an increase in myeloblasts. The patient died 5 days after admission, of cerebral hemorrhage.

Very few cases of refractory anemia, with or without excess of blasts, and no cases of classical ARSA, have been reported so far to terminate in Ph-negative CML [5]. One could consider the entities of MDS and Ph-negative CML as a continuous spectrum of diseases. At one end of the spectrum are processes characterized by major dysplasia and categorized as MDS. At the other end, excessive proliferation with myeloid differentiation defines cases of Ph-negative CML. Thus, our case suggests that ARSA may be included at one end of this spectrum, and a possible, although exceptional, evolution of ARSA into a Ph-negative CML with typical clinical and morphological features should now be considered.

E. Bandieri
C. Di Donato
F. Artioli
C. Carapezzi
First Medical Division, Ospedale "Ramazzini," Carpi, Italy

M. Luppi
T. Artusi
G. Torelli
Section of Hematology, Department of Medical Sciences, University of Modena, Modena, Italy

References

1. Lichtman MA, Brennan JK: Myelodysplastic disorders. In Williams WJ, Beutler E, Erslev AJ, Lichtman MA (eds): "Hematology." New York: McGraw-Hill, Inc., 1995, pp 257–272.
2. Beris P, Grof J, Miescher PA: Primary acquired sideroblastic and primary acquired refractory anemia. Semin Hematol 20:101–113, 1983.
3. Lokowicz DF, Myers TJ, Grasso JA, Albala MM: Sideroblastic anemia terminating in myelofibrosis. Am J Hematol 13:253–257, 1982.
4. Luppi M, Morselli M, Emilia G, Temperani P, Marasca R, Barozzi P, Selleri L, Torelli G: Spontaneous loss of Ph chromosome with maintenance of clonal hemopoiesis in an untreated patient with myeloproliferative disease and long survival. Genes Chromosomes Cancer 12:237–240, 1995.
5. Oscier DG: Atypical chronic myeloid leukaemia, a distinct clinical entity related to the myelodysplastic syndrome? Br J Haematol 92:582–586, 1996.

Residual Leukemic Blasts or Regenerating Normal Precursors? The Hematologist's Dilemma

To the Editor: A practical problem faced by hematologists is of differentiating acute leukemia from regenerating marrow especially with acute myeloid leukemia (AML). At present, the diagnosis of "remission" is usually made by morphological examination of postchemotherapy bone-marrow smears. Although this is satisfactory in most instances, it is not always possible to distinguish with absolute confidence residual leukemic blasts from regenerating marrow precursors. The use of growth factors may compound the problem by altering the maturation kinetics of hemopoietic precursors. A proper distinction is important, however, as it may influence clinical management decisions for the patient. A mistaken diagnosis of residual leukemia/relapse may lead to unnecessary and potentially dangerous chemotherapy, where a more conservative approach may be more reasonable, particularly in certain groups of patients. It is important for all clinical hematologists to be aware of this while treating AML patients. Morphological evaluation should be supplemented by other techniques.

The techniques useful for the detection of leukemic clones include cytogenetics, immunophenotyping, gene rearrangement studies, and the polymerase chain reaction for detection of molecular lesions [1]. Of these, immunophenotyping is the most widely available, is applicable to cases of acute myeloid leukemia, and appears to be useful. It is particularly applicable to cases with certain combinations of antigens. Examples are cases with coexpression of CD13/CD33/CDW65 with "aberrant" antigens such as CD2/CD7 and/or nuclear TdT [2], and of CD34 and CD4 or CD56 [3]. A recent study has also shown that leukemic myeloid cells may co-express CD-117 and CD15 whereas normal myeloid cells very rarely do so [4]. The other feature that may be usefully studied is the light-scatter pattern on flow cyometry, which can help in the identification of different types of AML blasts [5]. Two- or three-color analysis to demonstrate cell populations would also be very helpful.

The purpose of this letter is to draw the attention of all hematologists to the problem of distinguishing leukemic blasts from normal precursors and to stress the need for detailed immunophenotypic, cytogenetic, and, whenever possible, molecular analysis routinely in cases of AML at diagnosis and at appropriate phases during treatment. Finally, although immunophenotyping is not essential for diagnosis of otherwise typical AML, it should be performed for the above reasons, as well as to exclude biphenotypic/mixed-lineage leukemias [6].

H.S. Keshava-Prasad
University of Nevada School of Medicine, Las Vegas, Nevada

References

1. Campana D: Detection of minimal residual disease in leukemia and lymphoma. In: Ed. Brenner, MK "Recent Advances in Haematology," Vol 7. Edinburgh: Churchill-Livingstone, 1993, pp. 21–31.
2. Campana D, Coustan-Smith E, Behm FG: The definition of remission in acute leukaemia with immunologic methods. Bone Marrow Transplant 8:429, 1991.
3. Coustan-Smith E, Behm FG, Hurwitz CA, Rivera GK, Campana D: N-CAM (CD56) expression by CD3+ malignant myeloblasts has implications for minimal residual disease detection in acute myeloid leukemia. Leukemia 7:853, 1993.
4. Macedo A, Orfao A, Martinez A, Vidriales MB, Valverde B, Lopez-Berges MC, San Miguel JF: Immunophenotype of c-kit cells in normal human bone marrow: Implications for the detection of minimal residual disease in AML. Br J Haematol 89:338, 1995.
5. Vidriales MB, Orfao A, Lopez-Berges MC, Gonzalez M, Lopez-Macedo A, Garcia MA, Galende J, San Miguel JF: Light scatter characteristics of blast cells in acute myeloid leukaemia: Association with morphology and immunophenotype. J Clin Pathol 48:456, 1995.
6. Rowan RM, Bain BJ, England JM, Hyde K, Matutes E, Reilly JT, Stephens AD, Lewis SM, Shinton NK, Murphy MF, Wood JK: General Haematology Task Force

of BCSH-Immunophenotyping in the diagnosis of acute leukamias. J Clin Pathol 47:777, 1994.

Recurrent Reversible Nephrotic Syndrome During Therapy With Recombinant Interferon Alpha

To the Editor: Recombinant interferon alpha (rIFNα) is increasingly used in the treatment of hematological malignancies, solid tumors, viral infections, and AIDS-related complications. Toxicities commonly associated with IFN therapy include "flu-like" symptoms, gastrointestinal disorders, and central nervous system abnormalities. Severe renal toxicity has rarely been reported in IFN recipients. We describe a patient with renal-cell cancer in whom recurrent nephrotic syndrome developed after treatment with rIFNα.

A 54-year-old patient was admitted to our hospital because of back pain. On radiographic examination, he was found to have right renal cancer with multiple metastases of the liver, lungs, and skeleton. Following radical nephrectomy and radiotherapy of the bone metastases, the patient was treated with interferon-α2b (Intron A, Essex, Munich, Germany) at a daily dose of 1 million units (MU) subcutaneously. Over the ensuing weeks, the IFN dosage was increased to 3 and 5 MU daily (Fig. 1) Additional therapy consisted of biweekly injections of vindesine (5 mg) and slow infusions of pamidronate (60 mg). Except for the first days of IFN therapy, the patient did not receive comedication with paracetamol or other analgetics. A follow-up evaluation 7 months later revealed complete regression of all metastatic lesions. After 8 months of IFN therapy, the patient developed fatigue, breathlessness, and periorbital and peripheral edema. The serum albumin concentration was 2.l g/dl, and the 24-hr urinary protein excretion was 28.9 g/day. Urinary protein electrophoresis showed nonselective proteinuria. Microscopic examination of urinary sediment disclosed numerous hyaline and granular casts, as well as 5–15 red cells and leukocytes per high-power field. The serum creatinine was increased to 1.7 mg/dl. Viral and autoimmune serology, anti-phospholipid antibodies, anti-IFN antibodies, circulating immune complexes, and cryoglobulins were negative. There was no evidence of recurrent renal cancer on ultrasonography and chest radiograph. Renal vein thrombosis was excluded by Doppler ultrasound venography. Interferon was stopped, and the patient was treated with diuretics, albumin infusions, and high-protein diet, resulting in gradual improvement of abnormal clinical and laboratory findings. Treatment with vindesine and pamidronate was reinstituted without recurrence of renal abnormalities. Three months later, IFN therapy was resumed at a reduced dosage (1–3 MU interferon-α2a, Roferon A, Roche, Grenzach, Germany). Within 2 months, massive proteinuria and hypoalbuminemia occurred, but again normalized when IFN was withdrawn (Fig. 1).

While mild degrees of proteinuria have been described in up to 20% of IFNα recipients, severe renal disorders are rare. They manifest as oliguric and nonoliguric acute renal failure, nephrotic syndrome, or hemolytic uremic syndrome [1–3]. Among these complications, nephrotic syndrome appears to carry the best prognosis, because proteinuria is always reversible after withdrawal of IFN [4]. Our case report confirms this impression. In our patient, massive proteinuria recurred after reexposure to IFN, supporting a causal relationship between renal dysfunction and drug therapy. We conclude that close clinical monitoring and frequent urinalyses are required in each patient undergoing treatment with IFNα.

Carlo Aul
Horst Minning
Thomas Südhoff
Norbert Gattermann
Axel Heyll

Department of Internal Medicine, Hematology and Oncology Division, Heinrich Heine University, Dusseldorf, Germany

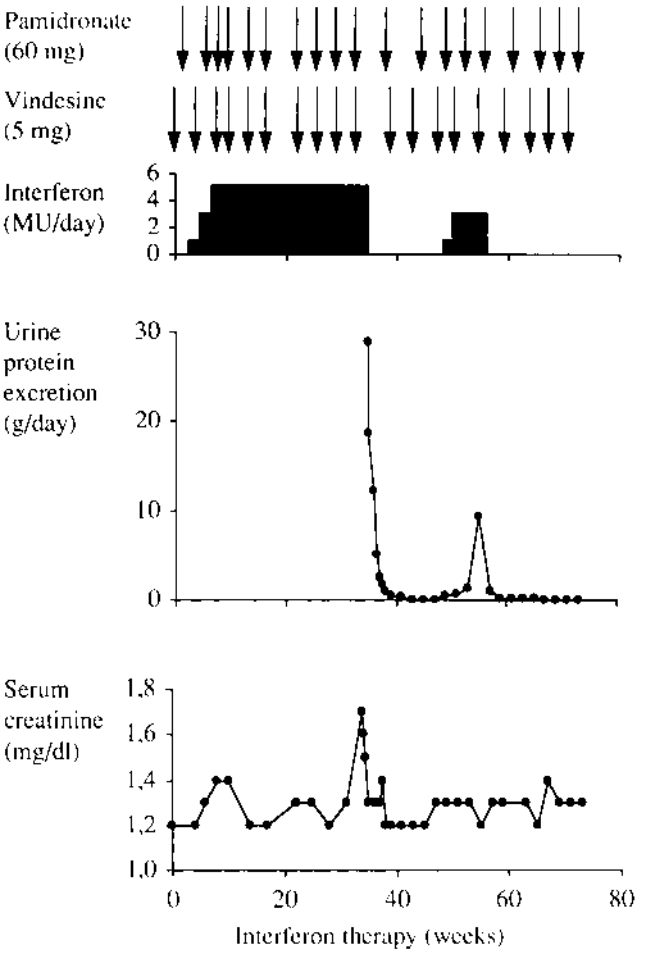

Fig. 1. Urinary protein excretion and serum creatinine levels during IFN-α therapy for renal cancer.

References

1. Averbuch SD, Austin HA, Sherwin SA, Antonovych T, Bunn PA, Longo DL: Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. N Engl J Med 310:32, 1984.
2. Noel C, Vrtovsnik F, Facon T, Noel-Walter MP, Hazzan M, Jouet JP, Bauters F, Lelievre G: Acute and definitive renal failure in progressive multiple myeloma treated with recombinant interferon alpha-2a: Report on two patients. Am J Hematol 41:298, 1992.
3. Stratta P, Canavese C, Dogliani M, Thea A, Degani G, Mairone L, Vercellone A: Hemolytic-uremic syndrome during recombinant α-interferon treatment for hairy cell leukemia. Ren Fail 15:559, 1193.
4. Aul C, Schneider W (eds): "Interferons—Biological Activities and Clinical Efficacy." Heidelberg: Springer, 1996, pp. 180–192.

Aleukemic Leukemia Cutis Preceding Overt Acute Myeloid Leukemia in Myelodysplastic Syndrome

To the Editor: We report on the case of a patient with myelodysplastic syndrome (MDS) who presented with aleukemic leukemia cutis preceding the developement of acute myeloid leukemia.

A 76-year-old man had been studied 4 years previously due to anemia and leukopenia. Peripheral blood showed: Hb, 11.8 g/l; WBC, 2.5×10^9/l (36% neutrophils, 53% lymphocytes, 8% monocytes, 1% eosinophils, and 2% basophils); Plt, 135×10^9/l. The rest of the studies performed (including serum biochemistry, serum immunoglobulins, hemoglobin electrophoresis, coagulation, vitamin B_{12}, folic acid, ferritin, and serum erythropoietin) were all within normal limits. Bone-marrow aspirate was hypercellular, with granulocytic hyperplasia and dysplastic features in the granulocytic and megakaryocytic series. Karyotype was normal (46,XY). Myelodysplastic syndrome, FAB refractory anemia subtype, was diagnosed. For 4 years the patient was followed up without relevant changes in peripheral blood. After this time he presented with progressive anemization and thrombocytopenia (86×10^9/l). Bone-marrow aspirate showed intense dyshemopoiesis in all series and 8% myeloblasts (myeloperoxidase positive), and a diagnosis of refractory anemia with excess of blasts was considered. One month later, erythemato-violaceous no pruriginous painless papules appeared in anterior and superior areas of the trunk. Biopsy of these lesions was performed, showing infiltration of the skin by myeloblasts (CD15+), and leukemia cutis was diagnosed. Three months later, due to a deterioration in peripheral blood (Hb 8.8 g/l, WBC 1.6×10^9/l (2% myelocytes, 2% metamyelocytes, 11% neutrophils, 73% lymphocytes, 8% monocytes, and 2% blasts), and Plt 72×10^9/l), a new bone-marrow aspiration was performed, and 55% blasts were observed; FAB type M2 leukemia was diagnosed. Considering the patient's age, treatment with low doses of Ara-C (10 mg/m^2/12 hr) was administered for 21 days without response (8% blasts in peripheral blood), though cutaneous lesions improved slightly. Ara-C doses were increased to 20 mg/m^2/12 hr for 12 days, but no response was observed. The patient died 10 days after termination of treatment due to a stroke.

Transformation into acute myeloblastic leukemia occurs in 6–37% of patients with MDS [1]. Cutaneous lesions in the course of acute leukemia is frequent (30–50%), mainly in myeloid leukemia. However, leukemia cutis (leukemic cell infiltration of the skin) occurs in <10% of cases, mostly in coexistence with overt leukemia [2,3]. This type of lesion is exceptional in MDS. No more than 40 cases of aleukemic leukemia cutis have been reported in the literature (the majority in acute granulocytic or monocytic leukemias) [3]. The appearance of these lesions varies greatly [3,4], from macules to tumors, and the diagnosis must be differentiated from other tumoral infiltrations of the skin, including atypical cutaneous B- or T-cell lymphoma and cutaneous metastasis [3]. Although possible advantages of treating MDS either before or after leukemization have not been recognized, in our opinion, and due to the fact that in a short period most of these aleukemic cases terminate in leukemia with a poor prognosis (death occurs in 50% of cases in <3 months after diagnosis) [4], treatment should be initiated immediately.

In conclusion, aleukemic leukemia cutis must be considered as an early manifestation of leukemic transformation [5] and an indicator of poor prognosis in MDS. Chemotherapy should be applied promptly to avoid this high risk of development of overt leukemia.

J.N. Rodríguez
A. Fernandez-Jurado
A. Navarro
M.L. Martino
D. Prados
Section of Hematology and Dermatology, Hospital "Juan Ramon Jimenez," Huelva, Spain

References

1. Sanz GF, Sanz MA, Vallespí T, Canizo MC, Torrabadella M, García S, Irriguible D, San Miguel JF: Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: A multivariate analysis of prognostic factors in 370 patients. Blood 74:395–408, 1989.
2. Kaiserling E, Horny HP, Geerts ML, Schmid U: Skin involvement in myelogenous leukemia: Morphologic and immunophenotypic heterogeneity of skin infiltrates. Mod Pathol 7:771–779, 1994.
3. Horlick HP, Silvers DN, Knobler EH, Cole JT: Acute myelomonocytic leukemia presenting as a benign-appearing cutaneous eruption. Arch Dermatol 126:653–656, 1990.
4. Aractingi S, Bachmeyer C, Miclea JM, Verola O, Rousselot P, Dubertret L, Daniel MT: Unusual specific cutaneous lesions in myelodysplastic syndromes. J Am Acad Dermatol 33:187–191, 1995.
5. Longacre TA, Smoller BR: Leukemia cutis. Analysis of 50 biopsy-proven cases with an emphasis on occurrence in myelodysplastic syndromes. Am J Clin Pathol 100:276–284, 1993.